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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,192	03/26/2004	Didier Communi	9409/2113C	1787

29933 7590 07/23/2007

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
07/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/811,192	**Applicant(s)** COMMUNI ET AL.
	Examiner Joanne Hama, Ph.D.	**Art Unit** 1632

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Applicant filed a response to the Final Action of February 27, 2007 on June 29, 2007. No amendments have been made to the claims submitted June 29, 2007. Claims 1-16 are withdrawn. Claim 18 is cancelled.

Claim 17 is under consideration.

Information Disclosure Statement

Applicant indicates that copies of each of the references cited on the IDS of the instant Application can be found in a second parent application, 10/753,695, filed January 8, 2004, as evidenced by the attached 1449 form from '695 in which the examiner considered all the references. In response, according to the copy of the IDS from '695, it appears that the Examiner has indicated that copies of the references have not been received, as the Examiner has indicated the references with an "X" and indicated at the bottom of the IDS that "X" was an indication of, "did not receive". Further, the Examiner has looked at '695 and has not found any of the cited references. Should Applicant wish to have the IDS considered, copies of the publications must be provided.

Maintained Rejections

35 U.S.C. § 101

Applicant's arguments filed June 29, 2007 have been fully considered but they are not persuasive. Applicant indicates that the specification discloses that the actions of extracellular nucleotides UTP are mediated by P2Y4 receptors and has asserted that P2Y4 receptors are a pharmacotherapeutic target for the treatment of cystic fibrosis. Applicant indicates that the

Office Action acknowledges that Ghanem et al. substantiates the potential of P2Y4 as a target for the treatment of intestinal complications in cystic fibrosis and that post-filing reference, Robaye et al. teach P2Y4 and its role in cystic fibrosis, i.e. the specific aspect of gastrointestinal (Applicant's response, page 5). In response, this is not persuasive. With regard to Ghanem et al., it is noted that Applicant had asserted that Ghanem et al. substantiate the potential of P2Y4 as a target for the treatment of intestinal complications in cystic fibrosis. The Office Action had not asserted the potential of P2Y4 as a potential target. It is noted that Ghanem et al. is post-filing art, of which, Ghanem et al.'s proposal that the claimed mice could be used to identify treatments for intestinal complications in cystic fibrosis does not provide support for the claimed mice at the time of filing, particularly because the specification does not teach that any knockout P2Y4 mice were made and that the mice exhibit any intestinal complications in cystic fibrosis (Office Action, May 19, 2006, page 7). As indicated in the Office Action, February 27, 2007, page 5, Robaye et al. teaches that at the time of filing, it was unclear what specific role P2Y4, compared to other family members was. As such, Robaye et al. indicate that the biological role of P2Y4 was unclear even at the time of filing.

Applicant indicates that the Office Action indicates that the specification does not provide guidance to specifically arrive at cystic fibrosis in the gastrointestinal system. Applicant indicates that cystic fibrosis was well known at the time of the invention to be a disease not limited to a particular tissue and nothing in the specification suggests limiting the use of P2Y4 targets to one particular tissue of cystic fibrosis (Applicant's response, page 5). In response, this is not persuasive. As indicated in the Enablement rejection, the art of transgenesis is unpredictable and subsequently, an artisan cannot predict what symptoms of cystic fibrosis the

claimed mouse would exhibit. Ghanem et al., post-filing art, indicates one specific aspect of cystic fibrosis that an artisan would need look for in P2Y4 knockout mice; nothing in the specification teaches that the gastrointestinal system is the system in which to examine the phenotype related to cystic fibrosis and thus, the specification at the time of filing does not enable an artisan to use the claimed mice as a model for disease. Applicant indicates that defects in CFTR destroy or reduce the ability of epithelial cells in the ariways, sweat glands, pancreas, and other tissues and refers to Frizell et al. (Applicant's response, page 6). In response, as evidenced by Ghanem et al., an artisan cannot predict that the claimed mice predictably exhibit symptoms of cystic fibrosis. Rather, as shown by Ghanem et al, an artisan must be told what particular aspect of the disease to look for in order to be able to use the claimed mice as a model of disease. With regard to Frizell et al., the reference has not been considered as a copy has not been provided.

With regard to Applicant indicating that knockout mice were routinely made at the time of filing and post-filing publications confirm the disclosed assertion that P2Y4 is a target for cystic fibrosis, the post-filing publications of P2Y4 and P2Y2 knockout mice, and the post filing date publications demonstrating the use of P2Y2 knockout mice as a therapeutic target for cystic fibrosis, Applicant respectfully submits that a transgenic mouse comprising a disruption in P2Y4 is patentably useful. In response, this is not persuasive. As discussed above, the specification at the time of filing, does not provide guidance that the claimed mice are models of any disease. Robaye et al., 2003, teach that the biological role of P2Y4 was unknown at the time of filing. Post-filing art indicates that when a knockout mouse was made, that the mouse had a particular phenotype associated with cystic fibrosis (Ghanem et al., 2005), which nothing in the

specification disclosed would be the phenotype exhibited by the mice, such that they could be used as a model of disease. Finally, Applicant indicates that the P2Y2 knockout mouse is a model of cystic fibrosis and is indicative that the P2Y4 knockout mouse is a model of cystic fibrosis. This is not persuasive since the role of P2Y4 was not known at the time of filing, see Robaye et al., 2003.

Thus, the claim remains rejected.

35 U.S.C. § 112, 1st parag., Enablement

Applicant's arguments filed June 29, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the only required limitation of claim is that the mouse be unable to produce a detectable level of P2Y4. This is not a complicated phenotype (Applicant's response, page 7). In response, this is not persuasive as nothing in the specification or the art provide guidance for using a transgenic mouse that does not express P2Y4. The claim, as written, encompasses mice that exhibit no symptom of disease and any mice that exhibit any symptom, unrelated to the gene disruption. As such, the use of these mice is unclear. The art teaches that knockout mice have a well-known utility as a model of disease. However, the art (e.g. Doetschmann and Racay) teaches that making mouse models of disease are unpredictable. Without guidance as to what phenotypes the claimed mouse exhibits and guidance as to what disease the phenotypes are related to, an artisan does not know how to use the claimed mouse. It is noted that the specification provides no guidance that any knockout P2Y4 mice were made. Applicant indicates that the technology of making knockout mice was well established and is an

established means of establishing animal models of disease (Applicant's response, page 7). In response, while the Examiner does not dispute that the art teaches how to physically make knockout mice and that some knockout mice are used as models of disease, the art indicates that an artisan cannot predict whether any knockout mouse is a model of disease, such that the knockout mouse can be used, see Office Action of May 19, 2006, pages 8-9, particularly Doetschmann and Racay references. Applicant indicates that the specification need not disclose what is well-known to those skilled in the art (Applicant's response, page 7). In response, the art teaches that predicting phenotypes of knockout mice and determining whether any of the phenotypes is related to a disease or disorder is not well known in the art, and thus, without guidance from the art or the specification, an artisan is not enabled for the claimed invention.

Applicant indicates that the high developed state of the art regarding knockout technology in mice, in combination with the identification and sequence of the gene encoding P2Y4 disclosed by the Applicant provides support for a substantial degree of predictability in arriving at the claimed mouse having a phenotype of an inability to produce a detectable level of P2Y4 (Applicant's response, page 7). In response, as discussed above, the use of a mouse that has no phenotype related to a disease or disorder or exhibits any phenotype unrelated to the gene disruption is not readily apparent. Applicant indicates that no more than routine experimentation is required to obtain the claimed mouse that has no detectable level of P2Y4 (Applicant's response, page 8). In response, while an artisan could carry out routine experimentation to determine whether the transgenic mouse does not express P2Y4, the specification does not provide any guidance for the use of the mouse that does not express P2Y4, particularly, if the mouse exhibits no phenotype related to a disease or disorder or exhibits phenotypes unrelated to

the gene disruption. The art teaches unpredictability in arriving at mouse models of disease and the specification does not teach that any mouse was made. Neither of these issues was addressed in the specification, and thus, the specification does not overcome these issues of unpredictability, such that an artisan could practice the claimed invention. Applicant refers to the teachings of Cressman et al., 1999, who teach P2Y2 knockout mice and indicate that the publication teaches techniques known at the time of filing and provide predictability and thus enablement for the claimed mice at the time of filing (Applicant's response, page 8). In response, Cressman et al. was not provided and thus, the Examiner has not considered the publication. With regard Applicant indicating that P2Y2 mice have been made, the Examiner does not dispute that an artisan can physically disrupt any gene of interest in a transgenic mouse. Rather, the issue of unpredictability is from obtaining a mouse with a phenotype that is related to the disrupted gene and to a disease or disorder. With regard to the art teaching a knockout of a related protein family member, knocking out one protein family member is not indicative that disruptions in other protein family members produce the same phenotype, see Office Action, February 27, 2007, page 5, reference to Robaye et al., who teach that it was unclear what specific role P2Y4 had in mice.

Applicant indicates it has been noted that the art accepted use of transgenic mice as animal models of disease, e.g. cystic fibrosis, is of record. Applicant indicates that MPEP 2107.03 indicates that Office personnel are warned to be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application (Applicant's response, page 8). In response, MPEP 2107.03 discusses special considerations for asserted therapeutic or pharmacological

utilities of a compound (i.e. drug) and has nothing to do with transgenic mice. In addition to this, it is noted that the use of the claimed mice was not apparent at the time of filing as Robaye et al., 2003, indicate that the biological activity of P2Y4 was unknown; thus, the utility of the claimed mouse as a model of cystic fibrosis was not known at the time of filing.

Thus, the claim remains rejected.

Priority

Applicant's arguments filed June 29, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the specification and art provide guidance for an artisan to arrive at the claimed invention, as described above (Applicant's response, page 9). In response, this is not persuasive, as the specification does not provide support for arriving at any knockout P2Y4 knockout mouse. See also Office Action, February 27, 2007, page 9. Thus, the priority of the Applicant is March 26, 2004.

35 U.S.C. § 102

Applicant's arguments filed June 29, 2007 have been fully considered but they are not persuasive.

Applicant indicates that Robaye et al. is not prior art as the Application has priority to 10/753,695 and 09/077,173 (now US patent 6,790,626). In response, this is not persuasive. See above for priority date determined for the instant Application.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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